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EDITORIAL COMMENT

Seizing the Science of Ultrasound

Beyond Imaging and Into Physiology and Therapeutics*

David D. McPherson, MD, FACC,†
Christy K. Holland, PhD‡
Chicago, Illinois; and Cincinnati, Ohio

But What is the Science?

This classic question of Dr. Francois Abboud, past President of the American Heart Association and Director of the Cardiovascular Research Center at the University of Iowa Hospitals and Clinics, had to do with modalities, including imaging modalities, that neither contributed to our understanding of cardiovascular pathophysiology nor therapeutically improved cardiovascular pathophysiology.

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Clinical diagnostic ultrasound (USD) (including cardiovascular) has been with us for approximately four decades. The imaging aspects of USD have significantly contributed to our knowledge of cardiovascular disease. Diagnostic USD has been used to answer questions concerning the timing of cardiac valve replacement (1,2); helped in understanding the pathophysiology of cardiac diseases, such as idiopathic hypertrophic subaortic stenosis (3); helped us understand how structural alterations occur in coronary and peripheral arteries with developing atherosclerosis (4,5); and helped to improve our understanding of coronary flow alterations in human atherosclerosis (6). By utilizing the physical principles of USD scattering, new agents have been developed that improve cardiovascular structural characterization, myocardial perfusion, and targeted molecular imaging of atherosclerosis using diagnostic USD (7,8). These are just a few of the thousands of applications that diagnostic USD has provided.

Although USD has matured as an imaging modality that is reliable and can be used to answer cardiovascular questions, it has much more potential. The science of USD, in addition to its imaging capability, also lies in its biologic effects.

The physical effects of ultrasound have been studied in vitro and in vivo in animal models and reviewed by Fowlkes and Holland (9,10). The physical effects of USD can be classified in two principal groups: 1) thermal and 2) mechanical. The effect of elevated temperature on tissue has been recognized, and the effects due to USD are not substantially different from those of any other localized heat source. The mechanical effects of USD include: 1) acoustic *radiation forces* on the structures within the body at both macroscopic and microscopic levels, resulting in exerted pressure and torque; 2) acoustically induced flow, or *streaming*; and 3) nucleation and pulsation of bubbles, or *cavitation*. The latter has been further utilized by developing therapeutic microbubbles, which encapsulate agents for targeted drug delivery and gene transfection into living cells upon exposure to USD (11–21). This application stems from the finding that the permeability of cell walls for large molecules (drugs and genes) is increased in the presence of USD and microbubbles (19).

In this issue of the *Journal*, Miyamoto et al. (21) expand the use of USD by demonstrating that low-level USD can cause vascular smooth muscle relaxation and arterial dilation in the coronary bed. Changes were measured by both intravascular USD and coronary angiography. Their results show that low-level USD has a similar effect to that of nitroglycerin in causing coronary artery vasodilation. Importantly, the effect is generalized, i.e., the transducer does not need to be directly over the coronary artery in question for vasodilation to occur; no significant temperature changes were noted; and limited pathologic analysis demonstrated a lack of gross changes in tissue structure over the USD exposure period. These data are important.

Why does this phenomenon occur? Ultrasound is known to have mechanical effects on tissue, both directly and by increasing shear stress on vascular tissues (acoustic radiation). Ultrasound can also cause cavitation effects when gas contrast agents, air, or similar interfaces are present. Although speculative in this study, USD most likely increases shear stress on endothelial cells, releasing nitric oxide, with resultant vasodilation. This mechanism is supported by other studies that demonstrate that the vasodilatory effects of USD can be blocked by the nitric oxide synthase inhibitor N^G-nitro-L-arginine methyl ester (22,23).

Similar to this study, the biologic effects of USD that are actively being investigated include all mechanical subtypes: radiation, streaming, and cavitation. These mechanical effects are intensively being investigated in the vascular and thrombolytic fields. Kilohertz frequency USD has been found to disrupt peripheral arterial and venous thrombi in animal models (24–26). The laboratory that presents the current article in the *Journal* has pioneered the use of the mechanical effects of USD to disrupt arterial atherosclerosis (27,28). Thrombolytic investigators have utilized the biologic effects of USD to enhance thrombolytics in peripheral thrombi and stroke models (29–37). Proposed mechanisms of USD-enhanced thrombolysis include: acoustic streaming alone, without cavitational effects; acceleration of fibrinolysis by increasing transport of reactants through a cavitation-

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From the †Northwestern University Medical School/Feinberg Cardiovascular Research Institute, Chicago, Illinois; and the ‡Department of Biomedical Engineering, University of Cincinnati, Cincinnati, Ohio.

related mechanism; or radiation effects that would alter the structure of the thrombus itself, allowing better penetration of lytic agents.

Of importance in the drug and gene therapeutic arena is the use of USD cavitational effects to enhance drug and gene delivery to pathologic cells for directed regional therapeutics and gene transfection (11–20). Drug and gene delivery can be enhanced more than 10-fold without deleterious consequences to the cell by the addition of therapeutic USD. These and other investigators are actively researching trapping the physical effects of USD to advance cardiovascular therapeutics.

So what is the utility and science of the study in the *Journal* by Miyamoto et al. (21)? Two utilities immediately come to mind. This technique may be used with angiography—especially quantitative coronary angiography—in better determining the physiologic severity of coronary stenoses. By giving therapeutic transcutaneous USD before and after angiography, areas of physiologic stenosis could be unmasked that were not apparent at the time of angiography. As the effect is widespread over the coronary arterial tree, selective intracoronary nitroglycerin might not be required.

Transthoracic USD could directly enhance intracoronary thrombolysis or, if given in conjunction with enhanced echogenic therapeutics, improve thrombolysis or drug and gene delivery. These would occur by both acoustic radiation forces and cavitational effects. As the stroke literature has demonstrated that these frequencies of USD can penetrate the skull and accelerate thrombolysis (32,33), the use of transthoracic USD for coronary interventions seems realistic.

So, Dr. Abboud: "This Is the Science of Ultrasound."

A novel, noninvasive methodology to evaluate coronary vascular flow/physiology has been demonstrated. By harnessing the physical effects of USD, we can physiologically evaluate and therapeutically affect vascular and biologic tissue. The door is now open to expand USD beyond the arena of diagnostic imaging.

Reprint requests and correspondence: Dr. David D. McPherson, Northwestern University Medical School, Galter 8-230, Northwestern Memorial Hospital, 251 East Huron, Chicago, Illinois 60611-2908. E-mail: d-mcpherson@northwestern.edu.

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